L1 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2004 ACS on STN
RN 2226-96-2 REGISTRY
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CN 1-Oxyl-2,2,6,6-tetramethyl-4-piperidinol
CN 2,2,6,6-Tetramethyl-1-oxy-4-hydroxypiperidine
CN 2,2,6,6-Tetramethyl-4-hydroxy-1-piperidinyloxy radical
CN 2,2,6,6-Tetramethyl-4-hydroxylpiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidin-1-oxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine 1-oxide radical
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine N-oxide
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine oxide
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-hydroxyl
CN 2,2,6,6-Tetramethyl-4-hydroxypiperidine-1-oxyl
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CN 2,2,6,6-Tetramethyl-4-hydroxypiperidinyl-1-oxyl
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CN 2,2,6,6-Tetramethyl-4-oxypiperidine-1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxide
CN 2,2,6,6-Tetramethyl-4-piperidinol 1-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol N-oxyl
CN 2,2,6,6-Tetramethyl-4-piperidinol nitroxide
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxy
CN 2,2,6,6-Tetramethyl-4-piperidinol-1-oxyl radical
CN 2,2,6,6-Tetramethylpiperidine-4-hydroxy-1-oxyl
CN 2,2,6,6-Tetramethylpiperidine-N-oxyl-4-ol
CN 2,2,6,6-Tetramethylpiperidinol-4-oxyl-1
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CN 4-Hydroxy-2,2,6,6-tetramethyl-1-piperidinoxy
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CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, PROUSDDR, RTECS*, TOXCENTER, ULIDAT, USPAT2, USPATFULL

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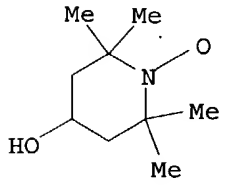

2171 REFERENCES IN FILE CA (1907 TO DATE)
60 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2174 REFERENCES IN FILE CAPLUS (1907 TO DATE)
24 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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CN 4-Hydroxy-2,2,6,6-tetramethyl-N-hydroxypiperidine
CN **Tempol H**
CN TOLH
FS 3D CONCORD
DR 87220-69-7
MF C9 H19 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, DETHERM*, TOXCENTER, USPAT2, USPATFULL
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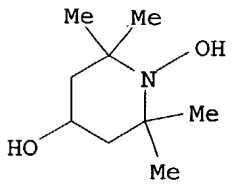

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

111 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
111 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

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- Tegretol
- Melanoma Cure

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Support Groups
Orphan Drugs

Ataxia Telangiectasia

Research sheds light on disorder

Mary Kugler, MSN, RN,BC
Guide to Rare/Orphan Diseases

Related Resources
- Internet links on **ataxia telangiectasia**

Elsewhere on the Web
- NINDS: **Ataxia Telangiectasia**
- A-T Children's Project

Researchers have discovered that both the gene mutation involved in **ataxia telangiectasia** and chromosome damage are responsible for the devastating effects of the disorder in the body. This research has offered a new insight into how complex the disease process may be, and what might be ways of reducing its symptoms.

What is ataxia telangiectasia?
Ataxia telangiectasia (a-TAX-ee-a TEL-an-gee-ek-TAY-sia) is a genetic disorder that affects the central nervous system, the eyes, skin, and immune system.

What are the symptoms?
The symptoms of **ataxia telangiectasia** are related to the body system affected.

- Central nervous system: loss of muscle control, leading to swaying of the head and trunk on standing; by age 10 children often need a wheelchair

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Muscular dystrophy
Neuro Disorders
Primary Immunodef.
Prion Diseases
Purpura
Respiratory
Skin Disorders
Storage diseases
Lupus

Subject Library

All articles on this topic

- Eyes: tiny red lesions, like spider veins, appear at the corners of the eyes and spread
- Skin: tiny red lesions, like spider veins, appear on the ears and roof of the mouth, across the face, and on the bridge of the nose. The lesions may spread to the hands and feet.
- Immune system: impaired immune system leaves child open to recurrent respiratory infections

Other symptoms may include delayed growth, difficulty speaking, and dry coarse hair and skin. Many children with **ataxia telangiectasia** develop cancers such as leukemia and Hodgkin's lymphoma.

How is it diagnosed?
Diagnosis is based on the symptoms the child has, especially the poor muscle control and the tiny red lesions on the eyes and face. The gene for **ataxia telangiectasia** has been identified, so genetic testing can be done to verify the diagnosis.

How is it treated?
There is at present no **cure** for **ataxia telangiectasia**, or way to slow down the progress of the disease. Treatment is aimed at relieving symptoms and trying to prevent respiratory infections, which are often the cause of death. Children with the disorder generally do not live beyond their teens or early 20s.

Information for this article was taken from:
- Calonje, D. (2001). **Ataxia-telangiectasia**. eMedicine, accessed at http://www.emedicine.com/oph/topics319.htm
- NINDS **Ataxia Telangiectasia** Information Page.

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Li-Fraumeni Syndrome

MA was worried. There was just too much cancer in her family, and she was concerned that she would be next.

Her older sister was only 18 years old when she developed a brain tumor, which required surgical intervention followed by radiation and chemotherapy. Her younger brother had died at 5 years of age from rhabdomyosarcoma (a rare cancer affecting skeletal muscle), despite being treated by pre- as well as postoperative chemotherapy accompanied with resection. Her mother had died of breast cancer at 43 years of age, despite mastectomy and chemotherapy at the time of diagnosis 4 years earlier. Her anxiety was only heightened when she considered her maternal family's history: an aunt with acute leukemia in adolescence, a grandfather who died from melanoma, and two first cousins who developed osteosarcomas in adolescence.

MA worried she might be a member of a "cancer family" that she recently read about in the newspaper. If so, she was not only concerned about her own risk of developing cancer but also about her two children, ages 6 and 10 years.

When F.P. **Li** and Joseph **Fraumeni** conducted a retrospective analysis of children who were diagnosed with or died from rhabdomyosarcoma (**Li** FP, **Fraumeni** JF Jr: Ann Intern Med 71:747-752, 1969), extended family histories of four children were significant for other cancers, particularly sarcomas, breast cancers, and leukemia at young ages.

Shortly thereafter, additional families with similar cancer clusters were independently reported. Mothers of children who had soft-tissue sarcomas were found to have a threefold increase in premenopausal breast cancer, compared to the general population.

Follow-up studies by **Li** and **Fraumeni** (Li FP et al: Cancer Res 48:5358-5362, 1988) found a higher incidence of second and subsequent cancers in surviving family members. Additional cancers were primarily adrenocortical carcinoma and brain tumors in first-degree relatives of children with soft-tissue sarcomas.

This was the first evidence of an actual inherited predisposition to cancer, and this inherited cancer **syndrome** was called **Li-Fraumeni syndrome**.

Li-Fraumeni syndrome has also been referred to as sarcoma, breast, leukemia, and adrenal gland (SBLA) **syndrome**.

The diagnostic criteria for **Li-Fraumeni syndrome** (**Li** FP, **Fraumeni** JF Jr: Ann Intern Med 71:747-752, 1969) are:

- a proband with a sarcoma diagnosed under 45 years of age,
- a first-degree relative with any cancer under 45 years of age, and
- a third family member who is a first-or second-degree relative with cancer under 45 years of age or a sarcoma at any age.

All three criteria must be met to establish the diagnosis.

Excess rates of melanoma, as well as cancers of the stomach, colon, pancreas, and esophagus, and gonadal germ cell tumors have also been reported in **Li-Fraumeni** families. The age at diagnosis of these cancers is usually younger than expected for the type of malignancy (Hartely AL et al: Cancer Genet Cytogenet 42:221-226, 1989; Strong LC, Williams WR: Am J Pediatr Hematol Oncol 9:99-103, 1987; Varley JM et al: Br J Cancer 76:1-14, 1997).

A **Li-Fraumeni**-like **syndrome** has also been described and shares some, but not all, of the features listed for **Li-Fraumeni syndrome**. Two definitions for **Li-Fraumeni**-like **syndrome** have been described.

Birch and colleagues' definition (Birch JM et al: Cancer Res 54:1298-1304, 1994) includes:

- a proband with any childhood cancer or sarcoma, brain tumor, or adrenal cortical tumor diagnosed under 45 years of age,
- a first- or second-degree relative with a typical **Li-Fraumeni syndrome** cancer (sarcoma, breast cancer, brain tumor, adrenal cortical tumor, or acute leukemia) at any age, and
- an additional first- or second-degree relative with any cancer under the age of 60 years.

Li-Fraumeni syndrome is inherited in autosomal dominant fashion. Studies have suggested that this is a highly penetrant cancer **syndrome**. Segregation analysis conducted on families with **Li-Fraumeni syndrome** revealed cancer risks of 50% by age 40 and up to 90% by age 60 (Lustbader ED et al: Am J Hum Genet 51:344-356, 1992). Another study calculated age-specific cancer risks and found a 42% risk between 0 and 16 years of age, a 38% risk between ages 17 and 45, and a 63% risk after age 45. The overall lifetime risk for cancer development was calculated to be 85% (Le Bihan C et al: Genet Epidemiol 12:13-25, 1995).

In children who are carriers of the **Li-Fraumeni** gene mutation, the estimated relative risk of developing cancer is 100 times the background rate.

The influence of environmental factors on cancer development in carriers of the **Li-Fraumeni** gene is unknown.

There are no benign markers that can predict cancer development or presence of the **Li-Fraumeni syndrome**. These cancers are not associated with any morphological or functional variations in affected individuals.

The component cancers of **Li-Fraumeni syndrome** tend to show up at different stages of life:

Age of Onset	Type of Cancer
Infancy	Development of adrenocortical carcinoma

Under 5 years of age Development of soft-tissue sarcomas

Childhood and young adulthood Acute leukemias and brain tumors

Adolescence Osteosarcomas

Twenties to thirties Premenopausal breast cancer is common

Treatment in the case of the **Li-Fraumeni syndrome** is cancer specific. There is no general treatment or **cure** for this **syndrome**:

Type of Cancer Treatment

Sarcoma Biopsy is essential since grading of the tumor is important in treatment

Osteosarcoma Management through amputation where possible and/or radiation and chemotherapy

Breast cancer Management through surgical intervention, radiation, and/or chemotherapy, depending on cancer stage

Brain tumors and

adrenocortical carcinoma Surgical intervention is used where possible; radiation and chemotherapy are used when necessary

Leukemia Treatment with chemotherapy

No surveillance measures, with the exception of breast cancer monitoring, have been shown to be effective in reducing morbidity or mortality among individuals with **Li-Fraumeni syndrome** or **Li-Fraumeni**-like **syndrome**.

Mammography and clinical breast examinations are effective in women over the age of 50 in the general population, but have not been shown to be beneficial for younger women at-risk in families with **Li-Fraumeni syndrome** or **Li-Fraumeni**-like **syndrome**. At-risk individuals and their physicians are encouraged to pay close attention to lingering illnesses, headaches, bone pain, abdominal discomfort, and any lumps or bumps that arise and have these symptoms evaluated promptly and thoroughly.

The following surveillance strategies for at-risk individuals in families with **Li-Fraumeni syndrome** or **Li-Fraumeni** like **syndrome** come from Varley and colleaugues (Br J Cancer 76:1-14, 1997).

Surveillance for at-risk children should include the following on an annual basis:

- a complete physical examination,
- urinalysis,
- complete blood count, and
- abdominal ultrasound examination.

Surveillance for at-risk adults should include:

- a complete physical examination once a year,
- twice yearly clinical breast examinations for women, and
- annual mammograms or a breast ultrasound examination for women (controversy exists regarding the use of mammography in women due to the possible radiation associated with TP3 mutations; see below).

  In any screening and treatment plans, consideration must be given to radiation exposure of affected individuals; radiation exposure may accelerate the malignancy process.

A candidate gene for the **Li-Fraumeni syndrome** is TP53 (p53), a tumor suppressor gene, located on chromosome 17p13.

- Deletions in TP53 in the tumors of **Li-Fraumeni** patients have been detected.
- Approximately 80% of mutations occur in exons 5□8.

The types of mutations in TP53 include:

- missense mutations, mostly in exons 5, 7, and 8 (86%),
- nonsense mutations (5%),
- deletions or insertions (8%), and
- splice-site acceptor mutations (?%).

Li-Fraumeni syndrome is rare, with fewer than 300 families reported worldwide. Germline mutations in TP53 are thought to account for less than 1% af all cases of breast cancer, 2% to 10% of childhood brain tumors (Felix CA et al: Med Pediatr Oncol 25:431-436, 1995: **Li** YJ et al: Int J Cancer 64:383-387, 1995), 50% to100% of childhood adrenocortical carcinomas (Wagner J et al: J Natl Cancer Inst 86:1707-1710, 1994; Varley JM et al: Br J Cancer 76:1-14, 1997), 3% of osteosarcomas (McIntyre JF et al: J Clin Oncol 12:925-930, 1994), 9% of rhabdomyosarcomas (Diller L et al: J Clin Invest 95:1606-1611, 1995), and 7% to 20% of multiple primary cancers occurring at an early age (Malkin D et al: New Engl J Med 326:1309-1315, 1992).

Testing for germline mutations in TP53 became available in 1993. Germline mutations are found in approximately 70% of **Li-Fraumeni** families (Varley et al: Cancer Res 57:3245-3252, 1997). This means that approximately one third of the families with classic **Li-Fraumeni syndrome** do not have germline mutations in the coding regions of TP53.

There are other molecular explanations for cancer development in **Li- Fraumeni** families when TP53 mutations are not detected:

- mutations in the promoter or regulatory regions of p53,
- mutations in intronic regions of p53, and
- other genes yet to be discovered.

Due to the rarity of **Li-Fraumeni syndrome**, direct sequence-based DNA testing of TP53 is available in a limited number of clinical laboratories and is often confined to exons 5 to 8, which is approximately 80% sensitive. A new chip-based DNA sequencing assay that detects the most common single base-pair mutations identified to date is available and has a sensitivity of approximately 90%. If the entire coding region of the TP53 is sequenced, sensitivity may approach 98%. See www.genetests.org for information

about laboratory testing for **Li-Fraumeni syndrome**.

The benefits of TP53 testing for **Li-Fraumeni syndrome** are:

- an opportunity to receive early, individualized screening if positive for a gene mutation;
- reassurance to those whose test results are negative for the mutation in their family; and
- increased accuracy of future planning.

There are drawbacks, however, to testing, and confusions that may arise:

- How does one interpret a negative result for TP53 testing in an apparent **Li-Fraumeni** family in which the gene mutation has not been identified?
- What is the meaning of a mutation in TP53 at a specific site but with unknown clinical significance?
- Test results provide a basis for potential insurance and employment discrimination.
- Confidentiality of testing and results of testing cannot be guaranteed.
- Screening measures following a positive test result may not yet enhance medical care or outcome.
- No correlation exists between the p53 genotype and clinical phenotype.

Testing raises other social and ethical considerations:

- Is testing of children and adolescence appropriate? See the National Society of Genetic Counselors resolution (1995) on genetic testing of children, as well as the American Society of Human Genetics/American College of Medical Genetics' position paper, Points to Consider: Ethical, Legal, and Psychological Implications of Genetic Testing in Children and Adolescents (1995).
- Testing can generate unexpected psychological stress.
- Is prenatal diagnosis for **Li-Fraumeni syndrome** an acceptable possibility?

Informed consent is a requirement before any genetic testing.

- Counseling of families on cancer risks associated with germline TP53 mutations can be difficult, because the morphology and site-, age-, and sex-specific incidence of cancers in carriers of such mutations is unknown.
- At present, there is no evidence that screening for early detection of cancers in children confers a survival benefit or a reduction in morbidity.
- In adults, it is likewise difficult to prove the efficacy of early detection of cancers, and the use of X-rays for at-risk persons is generally contraindicated because it may induce tumorigenesis.
- It should be mandatory that predictive testing for genetic susceptibility to cancer be carried out in medical centers with the appropriate expertise in clinical genetics and molecular technologies, with psychological assessment part of the standard protocol. The National Society of Genetic Counselors has published a statement regarding genetic testing for adult-onset disorders, which provides a detailed description of the pre-and post-test genetic counseling process, as well as potential issues (McKinnon WC et al: JAMA 278:1217-1220, 1997).

Help for families coping with **Li-Fraumeni syndrome** may be obtained by contacting:

- **Li-Fraumeni** Hotline (1-800-828-6622)
- National Cancer Institute (1-800-4-CANCER)
- American Cancer Society (1-800-ACS-2345)

- National Childhood Cancer Foundation (1-800-458-6223)